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IMMUNOLOGICAL RELATIONS OF A CHICKEN SARCOMA

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The employment of such terms as "sarcoma" and "tumor" throughout this paper is to be regarded rather as a concession to convenience than as indicating the possession of any definite idea regarding the material in question. The growth used in the following experiments is the first of that class to be reported by Dr. Peyton Rous, to whose courtesy our laboratory is indebted for the fowl from which the transplantations were made.

Because of the conflicting opinions regarding the nature of this tumor, it is a matter of some interest to ascertain whether chickens can be made resistant to it by previous treatment with embryonic fowl tissue, after the manner in which mice can be rendered refractory to mouse tumors with the embryonic material of their species.

A series of fowls were injected with hashed chicken embryo in amounts of from one to ten cubic centimeters, and inoculated with the sarcoma at periods varying from five to forty days later. Three weeks after the implantation of the tumor they were autopsied.

No reliable evidence of immunity was observed, as reference to the table will show. Since three treated chickens out of eight in the first group did not develop tumors, the experiment was repeated with double the amount of embryonic tissue; at the second trial the result was clean cut, none of the treated chickens being found resistant. The three other instances in which treated fowls did not develop tumors are probably chance occurrences, a view which is strengthened by the fact that Rous, also, has recorded quite recently his failure to immunize against this tumor.

On the other hand, the observation that some of the fowls engrafted with the sarcoma thirty-two and forty days after treatment, had smaller tumors than did those in the corresponding control groups, suggests that it may be possible, after all, to produce immunity to this growth, though it is evident that the development of the refractory state would take much longer than the ten days requisite in the mouse. It is intended to continue the experiment as soon as fertile eggs can be obtained in sufficient number.

TABLE I

Interval Between Treatment and Tumor Inoculation	Dose of Embryo Emulsion	Number of Chickens	Tumors	No Tumors
5 days	5.0 c.c.	8 treated, 10 controls[1]	10	0
			5	3
5 days	10.0 c.c.	6 treated, 6 controls	6	0
			6	0
10 days	1.0 c.c.	17 treated, 15 controls	15	0
			16	1
12 days	5.0 c.c.	10 treated, 11 controls	11	0
			10	0
14 days	2.0 c.c.	9 treated, 5 controls	5	0
			9	0
14 days	4.0 c.c.	5 treated, 2 controls	2	0
			5	0
25 days	5.0 c.c.	11 treated, 10 controls[1]	10	0
			10	1
28 days	2.0 c.c.	3 treated, 3 controls	3	0
			3	0
32 days	5.0 c.c.	3 treated, 5 controls	5	0
			2[2]	1
40 days	5.0 c.c.	7 treated, 11 controls	11	0
			7[2]	0

Even though it be finally proved impossible to immunize chickens against this tumor, the observation would be no unanswerable argument against its sarcomatous nature, for, in the first place, it is not known that the immunological reactions characteristic of the mouse have their counterpart in the chicken, and, secondly, mouse tumors are occasionally found against which no resistance can be produced. It could be interpreted, at best, only in conjunction with such facts as have been already ascertained, or as may be discovered in the future.

[1] Same controls used for both experiments.

[2] More small tumors than among controls.

Discussion.

Dr. Ewing: Considering the great frequency with which polyhedral cells are combined with spindle cells in human carcinomas and the clear evidence that these spindle cells are derived from the polyhedral cells, I have been surprised at the readiness of experimental pathologists to accept the conclusion that epithelial tumor processes are capable of exciting sarcomatous changes in the stroma. One of the first principles of tumor diagnosis is that considerable areas of spindle cells may occur in atypical carcinomas. This fact is not sufficiently recognized. I have examined many reports of the so-called carcino-sarcomatous growths and have been unable to satisfy myself that the spindle cell tissue was sarcomatous and not derived from epithelial tissue. In every case that I have seen outside the group of true mixed tumors the spindle cell areas have apparently been derived from polyhedral cells. I am not willing to express an opinion as to the significance of the tumors in lower animals; that should be left to those who are extremely familiar with the subject, but I have been fortunate enough to see two examples of so-called transformation of the stroma into sarcoma. In these two instances the specimens were submitted to me for proof of the sarcomatous change in the stroma. I did not however, reach this conclusion. I think the epithelium is transformed into spindle cells. I would not express a positive opinion without elaborate investigation, but I do not think that the conclusions drawn in this field have adequate support.

Dr. Rous: Last year Dr. Jones and I found three carcino-sarcomata among 135 mice with spontaneous tumors. The opportunities to study the condition were unusually good. The growths occurred in animals used in experiments on the influence of diet upon the development of recurrences and of disseminated fragments of spontaneous tumors. The mice were operated upon with incomplete removal of the tumor and the implantation of bits of it elsewhere. By the time these bits had begun to grow, or the tumor had recurred, a section of the primary growth was available for diagnosis.

Of the three carcino-sarcomata one seemed peculiar in the gross. It was a disc-shaped tumor in the mammary gland, giving retraction of the nipple. The second carcino-sarcoma was especially interesting. The primary growth was a pure carcinoma, the recurrence a mixed tumor and the growing grafts from the primary tumor consisted of pure sarcomatous tissue, although the material used for implantation had, so far as investigated, no such a constituent. All three of the carcino-sarcomata grew rapidly and were uninfluenced by diet.

Attempts were made to transplant the tumors; one of them grew rapidly for about ten days, but then underwent retrogression and was lost. Before our next attempt at transplantation we happened to read an article by Haaland, in which he mentions the general tendency of mouse sarcomata to retrogress after rapid initial growth. Accordingly, we re-transplanted the next carcino-sarcoma during the period of initial growth and were successful in propagating the tumor in this way. The growth regularly retrogresses after a few weeks. In the first generation it became a pure sarcoma.

Dr. Woglom says that in his opinion the occurrence of two sarcomatous tumors in one mouse suggests a special peculiarity of the tissues of this mouse. But is there not an alternative explanation? Multiple tumors are fairly frequent in the mammary glands of the mouse. We have noticed as many as five in one animal. Russell has pointed out that probably only one of such growths is primary, the others representing disseminations of it. In favor of this we have the fact that such multiple tumors are as a rule of identical histological structure. The mere fact that the tumors are widely separated is not good evidence against a metastatic origin for some of them.

We have made two attempts to immunize chickens against the chicken sarcoma with embryonal tissue, but both were unsuccessful. However, our experiments differed from Dr. Woglom's in that the tumor was implanted within a few weeks after the inoculation of the embryonal tissue. It seems very probable that the immunity induced by embryonal tissue is dependent on the absorption of the artificial teratoma produced by its growth. In the chicken such teratomata persist for a long time.

Dr. Woglom: In reply to Dr. Ewing, I can only reiterate my belief that those growths in the mouse which have been described as mixed tumors are actually carcinosarcomata. There occurs an entirely separate type of tumor, a pure carcinoma, composed partly of spindle-shaped epithelium, but here, as was pointed out, the transition between round and spindle-shaped cells is gradual, while in the carcinosarcomata it is abrupt.

Regarding the question of Dr. Rous, the possibility of one of the two tumors being a metastasis from the other was considered and disregarded.

Replying to Dr. Pappenheimer, a basement membrane was demonstrable in tumor 66.